Asymmetric Synthesis and Pharmacology of Methylphenidate and Its Para-Substituted Derivatives

Dung L. Thai,[†,‡] Michael T. Sapko,[†] Clara T. Reiter,[†] Donald E. Bierer,[‡] and James M. Perel*[,†]

Departments of Pharmacology and Psychiatry, University of Pittsburgh School of Medicine, E-1203 WPIC, 3811 O'Hara Street, Pittsburgh, Pennsylvania 15213, and Shaman Pharmaceuticals, Inc., 213 East Grand Avenue, South San Francisco, California 94080

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We report the first asymmetric synthesis of the individual enantiomers of methylphenidate (**1**). From *d*-pipecolic acid, the (2*R*,2′*R*) and (2*S*,2′*R*) enantiomers of **1** were obtained in >99% optical purity while the (2*S*,2′*S*) and (2*R*,2′*S*) enantiomers of **1** were derived from *l*-pipecolic acid in 96% optical purity. The versatility of this methodology is demonstrated with the synthesis of the (2*R*,2′*R*) and (2*S*,2′*S*) enantiomers of *p*-bromo and *p*-methoxy derivatives in similar yields and enantiomeric purities. Comparative neurochemical assessments of these synthesized enantiomers at purported dopamine, norepinephrine, and serotonin uptake sites along with locomotor activity studies in rats are also reported.

Methylphenidate (methyl 2-phenyl-2-(2′-piperidyl)-acetate) (**1**) is a commonly prescribed stimulant used in the treatment of attention deficit hyperactivity disorder (ADHD) in children and used for the treatment of narcolepsy and depression in adults.[1,2] Though it can exist as four possible stereoisomers, methylphenidate is administered to patients as a racemic mixture of threo diastereomers (Ritalin). The erythro isomers have been shown to exhibit very little therapeutic effect and contribute mainly to the toxic hypertensive effects of this drug.[3] In addition, in vitro and in vivo evaluation of the individual enantiomers of threo **1** obtained by recrystallization of the diastereomeric 1,1′-binaphthyl-2,2′-diyl hydrogen phosphate salts have shown that the pharmacological activity resides predominantly in the *d*-threo enantiomer (Figure 1).[4]

Despite a significant difference in the biological activity of *d*-threo **1** relative to its *l*-threo counterpart (eudismic ratio = 10),[4] there is presently no reported asymmetric preparation of the enantiomers of **1** in the literature. Previous methods for the synthesis of **1** have relied upon an original scheme which provided an 80:20 mixture of erythro/threo racemates which resulted from preferential erythro formation following platinum-catalyzed hydrogenation of a phenylpyridyl acetamide intermediate.[5] The mixture could then be epimerized to pure threo racemates. The preparation of threo bromo-, methoxy-, and hydroxy-substituted derivatives of **1** has been accomplished using this approach.[6,7] More recently, a modification of the methodology has been applied to the preparation of a series of aromatic-substituted derivatives of **1** in approximately six steps and 6−28% yield of a mixture of predominantly racemic threo isomers.[8] These derivatives were used in a structure−activity study comparing the effects of phenyl ring substitution of **1** on radioligand binding and neurotransmitter uptake by the dopamine transporter.[8] Our interest in methylphenidate-like compounds as alternative therapeutic agents in the treatment of ADHD in children and as potential chemical probes for studying the dopamine transporter lead us to develop an asymmetric preparation for the enantiomers of **1**.[9]

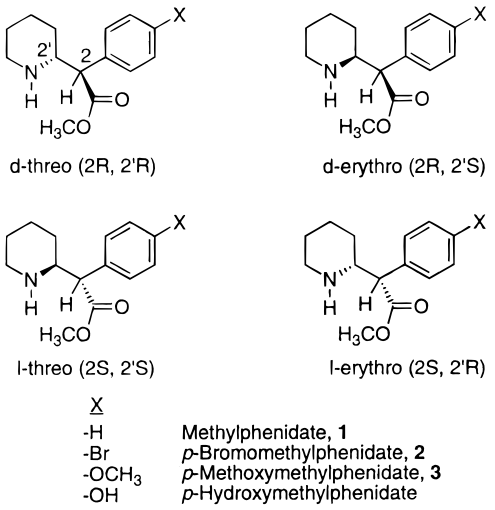

Figure 1. Chemical structures of the individual stereoisomers of methylphenidate and its para-substituted analogues.

We now present a method for the preparation of the optical isomers of **1** starting from chiral pipecolic acid in 27% yield and 99% enantiomeric purity for the *d*-threo enantiomer and in 30% yield and 96% enantiomeric purity for the *l*-threo enantiomer. This synthetic methodology also provides the individual erythro enantiomers, and its versatility is demonstrated with the preparation of the threo enantiomers of *p*-bromo **2** and *p*-methoxy **3** derivatives all in 96−99% enantiomeric purity (Scheme 1).

To demonstrate the role of aromatic substitution on the pharmacology of **1**, we compared the in vitro activities of the synthesized enantiomeric compounds to inhibit tritiated DA, *l*-NE, and 5-HT uptake into rat

* Address correspondence to this author at the University of Pittsburgh.
† University of Pittsburgh School of Medicine.
‡ Shaman Pharmaceuticals, Inc.

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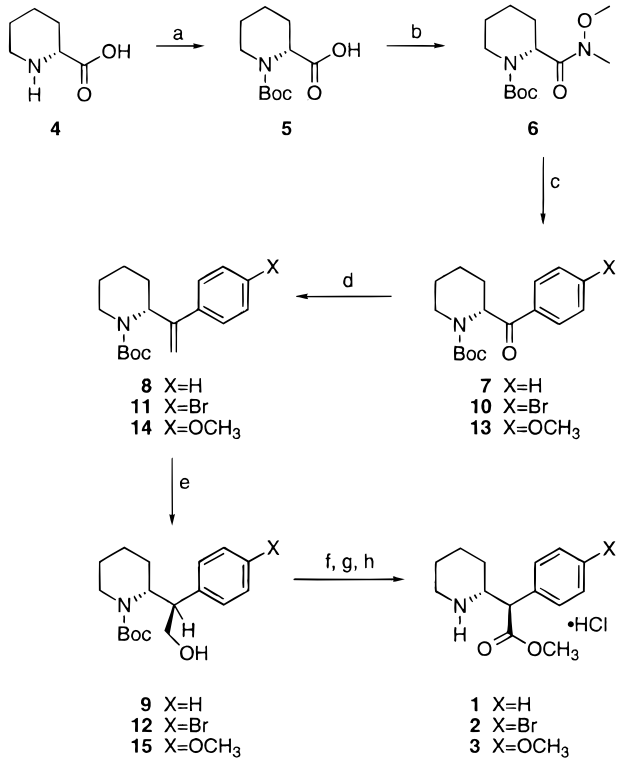
Scheme 1[a]



[a] Reagents: (a) $(Boc)_2O$, TEA; (b) BOP, TEA, *N*,*O*-Dimethylhydroxylamine hydrochloride; (c) *p*-X PhLi, then H^+/H_2O; (d) Methyltriphenylphosphonium bromide, $K^+OBu_t^-$; (e) (i) BH_3·THF, (ii) NaOH; H_2O_2; (f) PDC/DMF; (g) CH_2N_2; (h) methanolic HCl.

brain synaptosomes. As a screen of in vivo activity, the individual enantiomers of these derivatives were compared to the parent compound as stimulators of locomotor activity in rats following ip injection.

Chemistry

Our synthesis of the enantiomers of **1** relied upon pipecolic acid as the chiral educt. Optically pure pipecolic acid enantiomers were obtained by recrystallization of diastereomeric tartrate salts.[10] The amino acid was separated from the tartaric acid by ion-exchange chomatography and subsequently amino-protected with a Boc group in 97% yield.[11] To confirm the optical purity of the starting materials, the enantiomeric *N*-Boc pipecolic acids were derivatized to their *l*-α-phenylethylamide using (benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate (BOP) as a coupling agent and analyzed by a GC−MS method capable of resolving the diastereomeric derivatives. Both optical isomers of *N*-Boc pipecolic acid were found to be >98% enantiomerically pure.

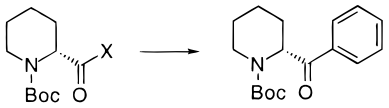
Our synthesis of enantiomerically pure **1** depended upon the preparation of optically pure aromatic amino ketone **7**. Prior literature on the preparation of optically pure amino ketones included two different strategies to aromatic products. Friedel−Crafts acylation of the corresponding N-protected amino acid chloride has been conducted on secondary and tertiary amines using benzene and anisole as electrophile acceptors.[12−14] However, this method lacks sufficient regiocontrol in the preparation of aromatic-substituted compounds and is not amenable to elaboration of nonphenyl aromatic systems. Organometallic addition to a suitably activated N-protected pipecolic derivative was an appealing approach which could provide better regiocontrol in the case of substituted aromatic derivatives and also allow the synthesis of a larger number of aromatic and heteroaromatic systems.

Though amino ketones of >99% enantiomeric purity have been obtained by organometallic methods, much of the work has concentrated on protected amino acid substrates containing abstractable carbamate protons. Buckley and Rapoport have shown that the presence of this abstractable proton is essential to maintaining configurational stability of the α-carbon by preventing deprotonation of the α-proton.[14] Nitrogen-protected pipecolic acid would not contain an abstractable carbamate proton which may then increase the likelihood of racemization under basic conditions. Cupps et al. have also evaluated several carboxylate-activating groups in the preparation of optically pure α,*β*-acetylenic ketones of alanine, methionine, and phenylalanine.[15] Alternatively, Rapoport has developed extensive methodology using amino acids protected with the extremely bulky 9-(9-phenylfluorenyl) (Phfl) group.[16−18] The amino acids protected in this way can be transformed to their equivalent α-amino aldehydes, ketones, and esters with no detectable racemization. Our initial approach to preparing an optically pure aromatic amino ketone of pipecolic acid attempted to take advantage of the configurational stability of *N*−Phfl-protected amino acids. This route was found to be less fruitful because of the difficulties in synthesizing *N*-(Phfl)-D-pipecolate *N*,*O*-dimethylamide. Even after obtaining the desired aromatic ketone by a circuitous route, the Phfl ketone was nonreactive toward Wittig olefination. Because of these initial problems, we decided to switch to a Boc protecting group.

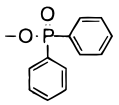
Using the results of the experimental and literature investigation as a starting point to obtaining protected ketone **7** and its aromatic-substituted derivatives in enantiomerically pure form, derivatives of **5** such as its *S*-thiopyridyl ester,[19,20] diphenylphosphinoyl anhydride,[21] and *N*-methoxy-*N*-methylamide[22] were treated with organometallic reagents under various reaction conditions. The results are summarized in Table 1. When *N*-methoxy-*N*-methylamide **6** was treated with 110 mol % of phenyllithium in THF at −23 °C, the isolated yield of **7** was 64%. Unfortunately, the product was found to be optically impure. The observed 10% racemization may have been the result of using a slight excess of the organolithium reagent. When the reaction was repeated in Et_2O at −23 °C with 100 mol % of organometallic reagent, the desired compound was obtained in enantiopure form and in 73% yield after recovery of starting material.

Once in hand, ketone **7** was converted to the chiral aromatic alkene **8** using a methylenetriphenylphosphonium ylide prepared from methyltriphenylphosphonium bromide and potassium *tert*-butoxide in THF at room temperature. With a slight excess (104 mol %) of Wittig reagent, the reaction did not go to completion, and the olefin was isolated in 50% yield. Increasing the amount of Wittig reagent to 150 mol % allowed clean transformation to a product which was easily purified by filtration though a short plug of silica gel in >90% yield.

Table 1. Reaction of Metallobenzene with Pipecolic Acid Derivatives

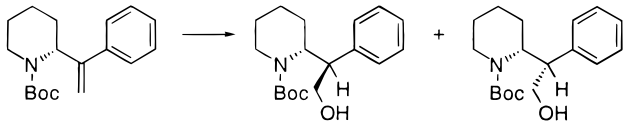


7

X	Organometallic, mol%	7 % Yield	Enantiopurity of 7
	PhMgBr, 110	8	ND[a]
	PhMgBr, 145	36	ND[a]
	Ph_2CuBr, 300	37	90%
	Ph_2CuBr, 500	57	90%
	PhLi, 110	64	90%
	PhLi, 100	47 (73[b])	99%
	PhMgBr, 300	22	ND[a]

[a]ND = Not Determined
[b]Yield based on recovered starting material

Table 2. Borane Reagent Effect on the Diastereoselectivity in the Hydroboration/Oxidation of *N*-Boc-phenylalkene (**8**)



8 (1R, 2R)-**9** *threo* (1S, 2R)-**9** *erythro*

borane reagent	mol %	temp, °C	yield, %	ratio threo/erytho
BH_3·THF	200	23	89	72/28
BH_3·Me_2S	200	23	73	59/41
(thexyl)-BH_2	200	0	46	35/65
(-)-IPC−BH_2	300	23	40	24/76
(+)-IPC−BH_2	300	23	55	100/0
$(cyclohexyl)_2$−BH	400	0	18	57/43

The transformation of olefin **8** to the diastereomers of alcohol **9** was critical in generating the second stereocenter of our target compound. It was important to achieve stereocontrol in the hydroboration/oxidation of **8** in order to obtain the desired threo enantiomer. Examples of remarkable 1,2- and 1,3-asymmetric induction in the hydroboration of acyclic terminal olefins have appeared in the literature.[23,24] In these cases, the diastereofacial bias of the reaction was influenced significantly by the proximal asymmetric center of the substrate and not necessarily by the borane reagents used.

We were interested in studying the 1,2-asymmetric inductive effects in our acyclic terminal olefinic system. Alkene **8** was treated with nonsubstituted, substituted, and chiral borane reagents. The results are shown in Table 2. Yields and diastereomer ratios were determined after isolation of the products by silica column chomatography. Though no simple model could explain the diastereomer ratios obtained, certain trends were still apparent. The combined yield of erythro and threo alcohols tended to decrease with increasing steric bulkiness of the borane reagents, suggesting that **8** is an extremely hindered alkene. This was apparent with dicyclohexylborane[25] which provided only 18% yield of the isomeric alcohols and with diisopinocampheylborane (not shown) which gave no isolatable product. The threo alcohol was favored with non- and disubstituted boranes while the erythro alcohol was the major isomer in the presence of the monosubstituted thexylborane. With the boranes, (+)- and (−)-IPC·BH_2,[26,27] the threo/erythro ratio was greatly influenced by the chirality of the hydroborating reagent. The ratio of the two diastereomers was 1:3 respectively in the presence of (−)-IPC·BH_2. On the other hand, only threo alcohol was isolated when our olefinic system was treated with (+)-IPC·BH_2. Hydroboration with BH_3·THF gave the highest overall yield of threo isomer (64%) while BH_3·Me_2S gave the highest overall yield of erythro isomer (30%).

Each isomeric alcohol was subject to PDC-mediated oxidation in DMF followed by treatment with excess ethereal diazomethane. The resulting *N*-Boc-methylphenidate was deprotected with 3 N methanolic HCl to give **1** as a white solid after recrystallization from EtOH/Et_2O in 60−65% yield from alcohol **9**. Assignment of threo and erythro stereochemistry was made by comparison of the products to standards by retention time on a GC and by ^1H NMR. Furthermore, subsequent pharmacological evaluation of these synthesized compounds provided results consistent with available literature and revealed that the assigned threo isomer was more active than its erythro counterpart (not shown).

The above methodology was applied to the preparation of the enantiomers of threo *p*-bromo (**2**) and *p*-methoxy (**3**) derivatives of **1**. Hydroxamate **6** was reacted with the appropriate para-substituted aryllithium under similar conditions as with the nonsubstituted organometallic reagent. Yields for the formation of the ketone varied between 28 and 56%. The *p*-bromo ketone **10** was isolated along with traces of nonsubstituted ketone **7** which may have been the result of lithium/halogen exchange on the aromatic moiety of **10** followed by protonation after aqueous quench. Conditions for preparation and isolation of subsequent enantiomeric para-substituted intermediates and products were similar to those of the parent compound. Enantiomeric purities of all the products were assessed by a GC−MS derivatization assay.

Pharmacology

Seven different compounds were evaluated for their ability to inhibit uptake of synaptosomal [^3H]DA and [^3H]*l*-NE. Table 3 provides calculated IC_{50} values based on graphical data for comparison of the activities of all compounds at the DA and NE transporter. Relative potency is defined in terms of racemic **1**. As shown in Table 3, the *d*-enantiomers of threo **1** and its derivatives were more potent than their *l*-counterparts at dopaminergic and noradrenergic synaptosomes. Optically pure *d*-threo **1** and *d*-threo **3** were approximately 1.3−2.6-fold more active than racemic **1** in DA and NE uptake assays. In the same assays, *d*-threo **2** was 18−20 times

Table 3. Comparison of the Abilities of Racemic and Enantiomeric **1** and Its Derivatives to Inhibit Synaptosomal Uptake of [^{3}H]DA and [^{3}H]NE

compound	dopamine IC_{50} (nM)[a]	eudismic ratio	norepinephrine IC_{50} (nM)[a]	eudismic ratio
racemic **1**	438 ± 18.4		171 ± 20.7	
d-threo **1**	171 ± 10.3	8.58	128 ± 34.7	6.84
l-threo **1**	1468 ± 112		876 ± 146	
d-threo **2**	22.5 ± 2.13	18.1	9.34 ± 0.84	26.6
l-threo **2**	408 ± 17.2		248 ± 38.2	
d-threo **3**	205 ± 10.8	17.5	73.0 ± 13.1	17.9
l-threo **3**	3588 ± 310		1305 ± 201	

[a] IC_{50} values were obtained from TABLECURVE (Jandel Scientific) after fitting the graphical data to a sigmoidal curve and are the mean ± SE of four experiments.

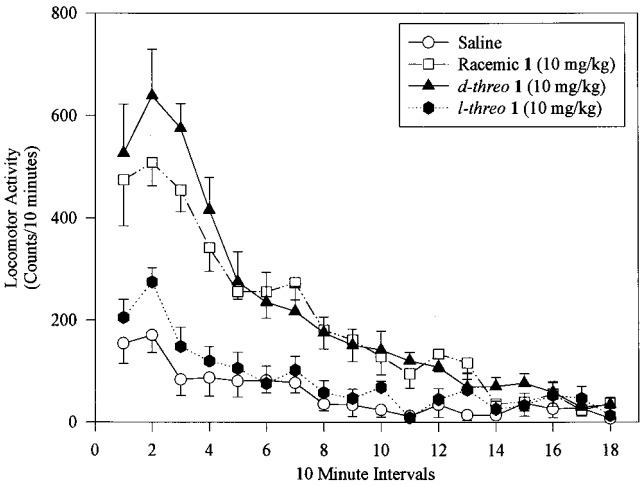


Figure 2. Effects of *d*-, *l*-, and *dl*-threo **1**·HCl on locomotor activity. Adult male rats were treated ip with drug after the animals had become accustomed to their surroundings. Each value represents the mean ± SE of six to nine experiments.

more potent than racemic **1**. Among the *l*-enantiomers, a majority of the compounds were found to be weaker than racemic **1** for [^{3}H]DA and [^{3}H]*l*-NE uptake inhibition. The exception was *l*-threo **2**, which exhibited in vitro synaptosomal dopamine activity close to that of racemic **1**. Very weak activity for inhibition of 5-HT uptake (IC_{50} > 5 μM) was noted for all compounds (not shown).

Eudismic ratios which were calculated for the NE and DA uptake experiments by dividing the IC_{50} for the *l*-isomer by the IC_{50} for the *d*-isomer of each enantiomeric pair are also listed in Table 3. Stereospecific effects for [^{3}H]DA and [^{3}H]*l*-NE uptake inhibition were 2−3-fold higher for both para-substituted methylphenidate analogues as compared to the parent compound. The highest ratios were seen with *p*-Br-methylphenidate.

A 180-min profile of locomotor activity of rats treated ip with saline, *d*-threo, *l*-threo, and racemic **1** is shown in Figure 2. The animals received an equivalent number of moles of drug (37 μmol) per kilogram of body weight, and activity counts for each successive 10-min period were recorded. In Figure 2, the locomotor activity of *d*-threo **1** was significantly greater than that of *l*-threo **1**, which was only slightly above saline treatment. Rats treated with racemic **1** exhibited locomotion between that of *d*- and *l*-threo **1**. Locomotor activity peaked 10−20 min after injection and was ∼650 counts/10 min for *d*-threo **1** and ∼500 counts/10 min for racemic **1**. After 50 min, activity levels were less than 300 counts/min for both compounds.

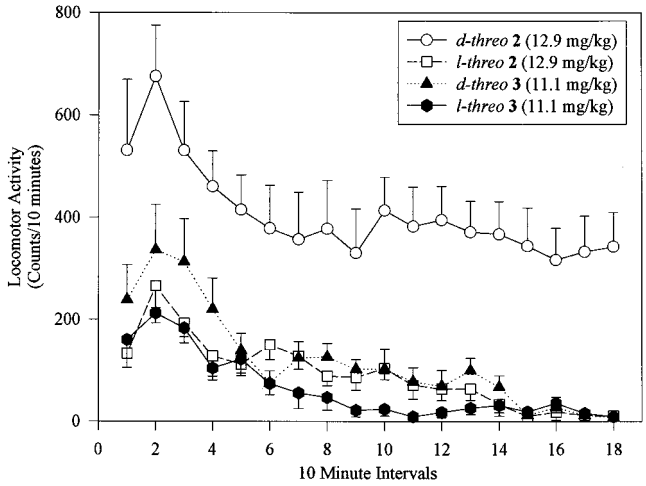


Figure 3. Effects of the *d*- and *l*-threo enantiomers of **2**·HCl and **3**·HCl on locomotor activity. Adult male rats were treated ip with drug after the animals had become accustomed to their surroundings. Each value represents the mean ± SE of six to nine experiments.

The optically active *p*-Br and *p*-OCH_3 derivatives of threo methylphenidate were also evaluated under the same conditions described above. As shown in Figure 3, the *d*-enantiomers of both analogues possessed greater inducing activity than their respective *l*-enantiomers. Peak values of 650−700 counts/10 min and 300−350 counts/10 min were observed 10 to 20 min after ip injection of *d*-threo **2** and *d-threo* **3**, respectively. After 50 min, activity associated with *d*-threo **3** treatment was less than 200 counts/10 min. On the other hand, rats treated with *d*-threo **2** had sustained locomotion greater than 350 counts/10 min for the entire 180-min test period. The *l*-enantiomers of both derivatives possessed profiles similar to that of *l*-threo **1**. Peak values did not exceed 300 counts/10 min, and mean activity counts were below 200 counts/10 min after 30 min.

A comparison of the *d*-isomers of **1** and its *p*-bromo derivative at lower doses was also undertaken to determine if the longer duration of locomotor induction by *d*-threo **2** relative to *d*-threo **1** could be reproduced. Figure 4 shows locomotor profiles of rats treated with 1.0 and 2.5 mg/kg of the two drugs via ip injection. For both drugs at 1.0 mg/kg, rats were not substantially more active than saline-treated animals. Locomotion after a higher dose of 2.5 mg/kg of *d*-threo **1** peaked at approximately 350 counts/10 min during the first 10−20 min time period. At 40 min postinjection, activity counts fell below 200 counts/10 min. The *p*-bromo derivative showed a greater peak activity (∼500 counts/10 min) than *d*-threo **1** with locomotion sustained above 200 counts/10 min for 130 min after a 2.5 mg/kg ip dose. Furthermore, maximal locomotion was observed during the 30−40-min time period after injection.

Discussion

In recent years, it has become recognized that the individual stereoisomers of biologically active chiral compounds may differ tremendously in pharmacological activity.[28] The threo enantiomers of **1** provide a clear

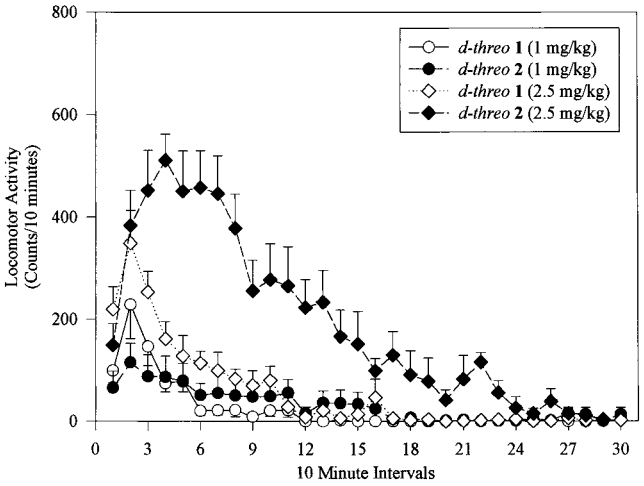


Figure 4. Dose effects of *d*-threo **1**·HCl and *d*-threo **2**·HCl on locomotor activity. Adult male rats were treated ip with drug (1.0 and 2.5 mg/kg in 1.0 mL/kg saline) after the animals had become accustomed to their surroundings. Each point represents the mean ± SE of six to nine experiments.

example of stereospecificity in which the *d*-isomer is 10 times more potent than the *l*-isomer for uptake inhibition of [^{3}H]DA and [^{3}H]*l*-NE into striatal and hypothalamic tissues, respectively.[4] In addition, the in vivo potency of *d*-threo **1** in inducing locomotor activity and potentiating the hypertensive effects of exogenously administered NE in rats is greater than the potency of *l*-threo **1**. In the present study, we examined this phenomenon with optically active *p*-Br and *p*-OCH_3 derivatives of **1**. These para-substituted analogues along with **1** were obtained by asymmetric syntheses, and their optical purities were assessed by GC−MS derivatization using (S)-MTPC.[29] Their pharmacological properties were then evaluated in both in vitro synaptosomal uptake assays and in vivo locomotor activity experiments.

The effects of aromatic ring substitution on in vitro synaptosomal activity had been examined in tropane as well as racemic methylphenidate analogues. Derivatives of WIN 35,065-2 substituted at the 4-position of the phenyl ring with a methoxy or bromine group had 2.8- and 12.7-fold higher affinity than its parent compound, respectively, for the dopamine transporter labeled with [^{3}H]WIN 35,428.[30] Recently, racemic threo derivatives of **1** substituted at various positions on the phenyl ring were prepared and evaluated for their ability to inhibit both the uptake of [^{3}H]DA into crude striatal membranes and the binding of [^{3}H]WIN 35,-428 to the DA transporter.[8] Among the compounds studied were the para brominated and methoxylated analogues of **1**. The authors found that bromine substitution increased the potency 8.5- and 12-fold for uptake and binding, respectively. Methoxy substitution, on the other hand, did not significantly alter the pharmacological activities for both parameters. The results for the bromine compounds were similar to previous reports which showed that racemic threo **2** had 8.5 times greater affinity for the dopamine transporter labeled with [^{3}H]WIN 35,428 as compared to threo **1**.[6] Comparing IC_{50} values in Table 3 obtained for the more active *d*-isomers, para bromination increased uptake inhibition 7.6-fold for DA and 13.8-fold for NE while para methoxylation decreased DA activity and increased NE activity both to a modest degree (<2-fold). Lower concentrations of all drugs were required to achieve the same effects for [^{3}H]*l*-NE uptake inhibition as compared to [^{3}H]DA uptake inhibition. Patrick et al. reported 10-fold greater potency against [^{3}H]NE transport relative to [^{3}H]DA transport.[4] Our studies of racemic **1** and the synthetic enantiomers revealed a difference of only 1.5−3.0 times. This may have been the result of our use of frontal cortical rather than hypothalamic synaptosomes in our in vitro experiments. Consistent with earlier work on bromine-substituted methylphenidate,[6] we found that both threo enantiomers of **2** along with **3** were inactive at the serotonin transporter (IC_{50} > 5 μM).

As defined by Hyttel et al., the more active enantiomer is called the eutomer, the less active enantiomer is called the distomer.[31] The eudismic ratio is a measure of degree of stereoselectivity, i.e., the ratio of activities of a pair of enantiomers. This ratio can be used to gauge the stereoselectivity of each enantiomer in a pair of racemates. Optical isomers of the phenylethylamine derivatives, amphetamine and deoxypipadrol, have been compared for their ability to affect neurotransmitter status in peripheral and central neural tissues.[32] Depending on the tissue used, the stereoselectivity of amphetamine sulfate for uptake inhibition of NE and DA ranged from none to moderate with ratios of 1 to 4. Effects of (+)-amphetamine on DA and NE release from the striatum was found to be stronger than those of (−)-amphetamine by a factor of 3. For deoxypipadrol, peripheral NE assays showed high selectivity with a ratio of 63. In crude synaptosomal preparations of rat cortex, hypothalamus, and striatum, the eudismic ratio for NE and DA uptake inhibition ranged from 13 to 31 with (*R*)-deoxypipadrol the more active enantiomer in both cases.

The difference in DA and NE uptake blockade by 99% optically pure *d*-threo **1** and by 92% optically pure *l*-threo **1** obtained in previous studies[4] was similar to the eudismic values of 8.58 and 6.84 obtained by us in similar synaptosomal studies. In addition, we found that para substitution of a bromine or methoxy group increased the differential stereospecificity of threo **1**. For the *p*-OCH_3 derivative, the increase in eudismic ratios at dopaminergic sites appears to be the result of a decrease in the potency of *l*-threo **3** for the DA transporter, while at noradrenergic sites, the effect can be attributed to an equivalent contribution of decrease in *l*-threo **3** and increase in *d*-threo **3** potencies. Bromination of methylphenidate at the para-position increased the NE and DA activity of both *d*- and *l*-threo **2**. The increase in stereospecificity can be explained in terms of a large rise in potency of the *d*-isomer as compared to the *l*-isomer when the para position of the compound is changed from a hydrogen to a bromine atom.

Locomotor activating effects of psychomotor stimulants are associated with CNS dopaminergic transmission.[33] Prior to this report, locomotor studies in rats were conducted on racemic and chiral **1** as well as racemic *p*-OCH_3 and *p*-Br derivatives. Comparing racemic and chiral threo **1** at a dose of 5.0 mg/kg ip, Patrick et al. found that rats treated with *l*-threo **1** were only slightly more active than saline-treated controls while racemic and *d*-threo **1**-treated animals possessed

locomotor activity profiles significantly greater than saline controls during the first 70−80 min of testing.[4] The racemic *p*-Br derivative has been tested in rats after a 20 mg/kg ip injection and has been reported to increase activity for approximately 200 min from time of dosing.[6] Under similar conditions and dosages, rats treated with racemic threo **3** possessed locomotion significantly greater than that of saline controls, lasting about 90 min.[34]

In our study, the activity of rats treated with racemic and chiral **1** along with its chiral analogues were compared at the same time under similar conditions. The *d*-*p*-Br compound was found to induce activity for the longest period of time, and its peak activity level was similar to that of *d*-threo **1** which did not sustain counts above 350 per 10 min after 50 min. Peak levels after ip injection with racemic **1** were not as high as those after treatment with *d*-threo **1**, but after 50 min, the time vs locomotion profile of both compounds were very similar. Of the *d*-enantiomers, the *p*-OCH_3 analogue possessed the lowest peak locomotor induction at approximately 350 counts/10 min, and its counts were only slightly above baseline at 50 min.

Because of the strong observed activity of rats treated with a high dose of *d*-threo **2**, we were interested in the lower dose effects of this drug relative to *d*-threo **1**. Our comparison of *d*-threo **1** and *d*-threo **2** showed that the bromo derivative could sustain rodent locomotion nearly three times as long as the parent compound after an ip injection of 2.5 mg/kg. At a lower dose of 1.0 mg/kg, the inducing ability of both stimulants was not substantially different from saline controls. Levels of drug in the blood and at the site of pharmacological action in the brain may have been below threshold. The dose of these two drugs required to elicit a response in rats was probably somewhere between 1.0 and 2.5 mg/kg.

The locomotor results obtained in this study are difficult to compare quantitatively to previous studies because of the inherent variability in measuring rat behavior with two different systems. Nonetheless, the trends for *d*-threo vs *l*-threo vs racemic **1** reported by Patrick et al.[4] were reproduced in our laboratory. Furthermore, previous experiments in a limited number of rats have shown that racemic threo **2** at 20 mg/kg ip can induce a longer duration of activity[6] as is revealed in our studies with approximately half as well as one-eighth the dose of pure *d*-threo **2**. In prior studies, no strong conclusions on the activity of **3** could be made relative to other compounds because no direct controlled comparisons were reported.[34] The present data argues strongly that *d*-threo **3** is a weaker stimulant of locomotion in rats than racemic, *d*-threo **1** and *d*-threo **2**.

The relationship between in vitro synaptosomal potency and in vivo locomotor activity in terms of maximal locomotor counts or duration of locomotor induction is not directly correlative. The apparent discrepancy between in vitro and in vivo activity is highlighted in the cases of *d*-threo **2** and *l*-threo **3**. Although threo **3** possesses a relative potency of 2.1 and 2.3 for [^{3}H]DA and [^{3}H]*l*-NE uptake inhibition, it does not act as strongly as racemic **1** in locomotion assays. Similarly, *l*-threo **2** potency is within a 2-fold difference for synaptosomal uptake blockade relative to racemic **1**, but again, the compound is only weakly stimulating in rats. The phenomenon described above may be the result of metabolism and/or distribution of these two compounds. Aoyama et al. showed that rats treated iv with the pure threo enantiomers of **1** possessed very similar blood pharmacokinetics but greatly different locomotor profiles and maximal striatal DA levels.[35] The same authors found that regional brain-to-plasma concentrations of *d*-threo **1** at 120 and 240 min were higher than that of *l*-threo **1**.[36] In part, selective binding and distribution are responsible for the stereoselective pharmacological effects of threo **1** enantiomers. Enantioselective presystemic metabolism provides additional insight into the overall stereoselective behavior of an oral or ip dose of threo **1**. In contrast to rats, an oral dose of racemic **1** in humans is presystemically and enantioselectively metabolized to ritalinic acid by the gut and liver to give 20−30% bioavailability of an approximate 4:1 *d*-threo to *l*-threo isomer ratio.[37] The bioavailability of racemic **1** in rats obtained by administration of identical oral and iv doses is 0.22.[38] In addition, parahydroxylation in rats occurs more extensively than in humans and is exclusively seen with *l*-threo **1** but not *d*-threo **1** after ip injection of the pure enantiomeric forms.[39] For *l*-threo **2**, the carbon to bromine bond may be labile to oxidation by rat liver microsomes leading to the formation of a *p*-hydroxy metabolite which is sequestered by the liver and also does not penetrate the blood−brain barrier to a significant extent.[7] Discrepant in vitro and in vivo results for *d*-threo **3** may be the result of poor CNS penetrability of the untransformed drug and/or sequestration by peripheral organs. Additional pharmacokinetic/metabolic studies are currently being pursued to identify factors which may be responsible for the locomotor activity profiles of the synthesized compounds.

Conclusion

We report the first asymmetric preparation of the four enantiomers of methylphenidate as well as the threo enantiomers of its *p*-bromo **2** and *p*-methoxy **3** derivatives. From *d*-pipecolic acid, the (2*R*,2′*R*)-enantiomers of **1**, **2**, and **3** along with the (2*S*,2′*R*)-enantiomer of **1** were synthesized in >99% optical purity and 10−27% overall yield. The (2*S*,2′*S*)-enantiomers of **1**, **2**, and **3** along with the (2*R*,2′*S*)-enantiomer of **1** were prepared from *l*-pipecolic acid in 96% optical purity and 8−30% overall yield. The synthetic methodology described above can be applied to the preparation of novel aromatic methylphenidate derivatives. As predicted from previous work on enantiomeric **1**, the *d*-threo isomers of the parent compound and its derivatives were more potent inhibitors of synaptosomal [^{3}H]DA and [^{3}H]-*l*-NE uptake than their corresponding *l*-threo isomers. The two para-substituted derivatives, *d*-threo **2** and *d*-threo **3**, were found to be 2−20 times more potent than racemic **1** as evidenced by their lower IC_{50} values for [^{3}H]DA and [^{3}H]*l*-NE uptake inhibition. Comparison of the locomotor activities of the *d*-isomers of methylphenidate and its *p*-substituted derivatives in rats revealed that *d*-threo **2** was longer acting in vivo than *d*-threo **1** while *d*-threo **3** was the weakest of the three stimulants. These enantiomeric derivatives may have potential as attention facilitators in the treatment of pediatric and adult ADHD.

Experimental Section

Chemistry. THF was distilled over K/benzophenone, and triethylamine (TEA) was distilled over CaH_2. Diphenylphosphinic chloride was distilled under reduced pressure. Anhydrous Et_2O and CH_2Cl_2 were obtained from Aldrich. *N*,*O*-Dimethylhydroxylamine hydrochloride was purchased from TCI America. Pipecolic acid was obained from Acros Organics as a racemic mixture and resolved into its *d*- and *l*-enantiomers by recrystallization of its diastereomeric tartrate salts.[10] Anisoyllithium was prepared by the methods of Berree et al.[40] and used as a 0.43 M ethereal solution, while (*p*-bromophenyl)-lithium was prepared by the methods of Trepka and Sonnenfeld used as a 0.37 M ethereal solution.[41] BOP was prepared by the methods of Castro.[42] Thiopyridyl chloroformate was used as a 0.19 M solution in CH_2Cl_2 and prepared according the methods of Corey.[19] All moisture-sensitive reactions were performed under a static Ar atmosphere (balloon) using dry solvents. Organic layers from aqueous extractions were dried over anhydrous $MgSO_4$ unless otherwise indicated and flash evaporated under reduced pressure. Thin layer chomatography was performed on Whatman 250 μ F_{254} silica gel plates and visualized by UV or by treatment with 0.2% ninhydrin in acetone followed by heating at 160 °C. Liquid chomatography was performed on Whatman 230−400 mesh silica gel using air pressure. GC−MS was obtained on a Hewlett-Packard 5890 GC, 5970 mass selective detector (MSD) with a capillary direct interface, and 5940 HP−UX Chemstation. The MSD includes a Phasor HED (high-energy dynode). The column was an HP Ultra-2 (cross-linked 5% phenyl methyl silicone) fused silica capillary column, 12 m length, 0.20 mm i.d.., film thickness 0.33 mm. Analytical conditions include the following: initial column oven temperature of 130 °C increased at a rate of 7 °C/min to a final temperature of 290 °C. The injector temperature was 290 °C, the detector temperature 300 °C, the helium (carrier gas) column flow (linear velocity) 38 cm/s, septum purge flow 1.8 mL/min, purge vent flow 61 mL/min. MSD was set on scan mode for masses between 25 and 800 *m*/*e*. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or CD_3OD as noted at 300 and 75 Hz, respectively, and coupling constants are reported in hertz. Melting points are uncorrected. Elemental analyses were performed by Quantitative Technologies, Inc.

***N*-(*tert*-Butyloxycarbonyl)-D-pipecolic Acid (5).** To a vigorously stirred solution of *d*-pipecolic acid (2.0 g, 15.5 mmol) and TEA (2.4 mL, 17.2 mmol) in methanol (22 mL) at 50 °C was added di-*tert*-butyl dicarbonate (7.12 mL, 31.0 mmol) via syringe. Stirring was continued at 50 °C for 5 min and at rt for 1 h. The reaction mixture was then concentrated to an oily residue and suspended between EtOAc (75 mL) and saturated $NaHCO_3$ (75 mL). The organic layer was extracted with saturated $NaHCO_3$ (2 × 25 mL) and H_2O (25 mL). Combined aqueous layers were brought to pH = 2.0 with 3 M HCl and immediately extracted with EtOAc (50 mL, 2 × 25 mL). The combined organic layers were washed with dilute HCl, dried, filtered, and evaporated to give 3.45 g of (*R*)-**5** as a white solid (97% yield): mp 123−124 °C; $[\alpha]^{20}_D$ +59.5° (*c* 2.06, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 11.34 (s, 1H), 4.83 (d, J = 13.5, 1H), 3.94 (m, 1H), 2.93 (m, 1H), 2.21 (br s, 1H), 1.66 (br s, 3H), 1.44 (s, 9H), 1.28 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 177.8, 156.2, 80.36, 53.61, 42.11, 28.34, 26.63, 24.60, 20.74. Anal. ($C_{11}H_{19}NO_4$) C, H, N.

***N*-(*tert*-Butyloxycarbonyl)-L-pipecolic acid (5):** 98% yield; mp 123−124 °C; $[\alpha]^{20}_D$ −58.7° (*c* 3.42, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 11.42 (s, 1H), 1.65 (br s, 3H), 1.43 (s, 9H), 1.30 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 177.8, 156.1, 80.36, 53.57, 42.09, 28.31, 26.60, 24.74, 20.77. Anal. ($C_{11}H_{19}NO_4$) C, H, N.

***N*-(*tert*-Butyloxycarbonyl)-D-pipecolate *N*-(Methylmethoxyl)amide (6).** (*R*)-Acid **5** (7.0 g, 30.6 mmol) was dissolved in CH_2Cl_2 (94 mL), and *N*,*O*-dimethylhydroxylamine hydrochloride (3.57 g, 36.6 mmol) and TEA (15.0 mL, 108 mL) were added. Solid BOP (14.8 g, 33.6 mmol) was then added and the reaction mixture stirred for 6 h. The reaction mixture was diluted with CH_2Cl_2 (450 mL) and transferred to a separatory funnel containing 1 M HCl (60 mL). The organic layer was washed consecutively with $NaHCO_3$ (3 × 60 mL), brine (2 × 60 mL), and H_2O (2 × 60 mL). Drying over $MgSO_4$, filtration, and evaporation provided an oil which was chomatographed on silica gel with 25% EtOAc in hexanes as eluant to give 7.74 g of (*R*)-**6** as a colorless oil (93% yield): $[\alpha]^{20}_D$ −1.35° (*c* 2.89, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 4.94 (d, J = 9.0, 1H), 3.87 (m, 1H), 3.72 (s, 3H), 3.39 (m, 1H), 3.14 (s, 3H), 1.96 (d, J = 5.2, 1H), 1.66 (m, 2H), 1.62 (m, 1H), 1.44 (s, 9H), 1.24 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 173.2, 155.9, 79.40, 61.06, 50.47, 42.09, 31.89, 28.24, 26.27, 24.74, 19.44. Anal. ($C_{13}H_{24}N_2O_4$) C, H, N.

***N*-(*tert*-Butyloxycarbonyl)-L-pipecolate *N*-(methylmethoxyl)amide (6):** 94% yield; $[\alpha]^{20}_D$ +1.88° (*c* 4.30, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 5.05 (br s, 1H), 3.91 (m, 1H), 3.76 (s, 3H), 3.44 (m, 1H), 3.18 (s, 3H), 1.98 (d, J = 3.4, 1H), 1.67 (m, 2H), 1.57 (m, 1H), 1.44 (s, 9H), 1.24 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 172.8, 155.5, 78.84, 60.61, 50.10, 41.71, 31.47, 27.81, 25.86, 24.32, 19.03. Anal. ($C_{13}H_{24}N_2O_4$) H, N; C: calcd, 57.33; found, 58.62.

(2*R*)-*N*-(*tert*-Butyloxycarbonyl)piperidin-2-yl Phenyl Ketone (7). A solution of (*R*)-hydroxamate **6** (400 mg, 1.47 mmol) in Et_2O (6.3 mL) was brought to −23 °C under an inert atmosphere, and 2.0 M phenyllithium in hexanes (735 μL, 1.47 mmol) was added dropwise via syringe over 15 min. Stirring was continued at −23 °C for 3 h, after which the reaction mixture was poured into an ice-chilled 1 M KH_2PO_4 solution (20 mL). The aqueous layer was extracted with EtOAc (4 × 15 mL), and the combined EtOAc layer was dried, filtered, and evaporated. Chomatography over silica gel eluting with 7.5−20% EtOAc in hexanes gave 200 mg of ketone (*R*)-**7** as a white solid along with 143 mg of recovered starting material (47% yield, 73% yield based on recovered starting material): mp 126−128 °C; $[\alpha]^{20}_D$ +25.8° (*c* 1.06, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.87 (m, 2H), 7.50 (m, 1H), 7.41 (m, 2H), 5.55 (d, J = 11.7, 1H), 3.89 (m, 1H), 3.12 (m, 1H), 2.06 (m, 1H), 1.78 (m, 1H), 1.56 (m, 2H), 1.43 (s, 9H), 1.36 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 200.9, 155.8, 135.8, 132.8, 128.5, 128.1, 79.94, 56.09, 42.57, 28.29, 26.18, 24.95, 19.92. Anal. ($C_{17}H_{23}NO_3$) C, H, N.

[(2*S*)-*N*-(*tert*-Butyloxycarbonyl)piperidin-2-ylphenyl ketone (7): 47% yield as a white solid, 88% based on recovered starting material: mp 123−125 °C; $[\alpha]^{20}_D$ −24.6° (*c* 2.03, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.87 (m, 2H), 7.49 (m, 1H), 7.41 (m, 2H), 5.55 (d, J = 11.6, 1H), 3.91 (m, 1H), 3.13 (m, 1H), 2.06 (m, 1H), 1.78 (m, 1H), 1.57 (m, 2H), 1.42 (s, 9H), 1.36 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 200.9, 155.7, 135.8, 132.8, 128.5, 128.1, 79.88, 56.01, 42.53, 28.24, 26.14, 24.91, 19.85. Anal. ($C_{17}H_{23}NO_3$) C, H, N.

(2*R*)-*N*-(*tert*-Butyloxycarbonyl)piperidin-2-yl 4-bromophenyl ketone (10): 33% yield as a white solid, mp 124−125 °C: $[\alpha]^{20}_D$ +29.8° (c 1.31, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.78 (m, 2H), 7.56 (m, 2H), 5.48 (d, J = 11.9, 1H), 3.90 (m, 1H), 3.03 (m, 1H), 2.07 (m, 1H), 1.78 (m, 1H), 1.59 (m, 2H), 1.44 (br s, 11H); ^{13}C NMR ($CDCl_3$) δ 200.0, 155.7, 134.6, 131.9, 129.8, 127.9, 80.23, 56.10, 42.72, 28.34, 25.94, 24.98, 19.94. Anal. ($C_{17}H_{22}NO_3Br$) C, H, N.

(2*S*)-*N*-(*tert*-Butyloxycarbonyl)piperidin-2-yl 4-bromophenyl ketone (10): 28% yield as a white solid; mp 124−126 °C; $[\alpha]^{20}_D$ −26.3° (*c* 1.01, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.79 (m, 2H), 7.58 (m, 2H), 5.49 (d, J = 11.9, 1H), 3.91 (m, 1H), 3.04 (m, 1H), 2.08 (m, 1H), 1.80 (m, 1H), 1.61 (m, 2H), 1.45 (br s, 11H); ^{13}C NMR ($CDCl_3$) δ 200.1, 155.7, 134.6, 131.9, 129.8, 128.0, 80.28, 56.25, 42.77, 28.40, 26.05, 25.07, 19.99.

(2*R*)-*N*-(*tert*-Butyloxycarbonyl)piperidin-2-yl 4-methoxyphenyl ketone (13): 46% yield as a white solid; mp 98−99 °C: $[\alpha]^{20}_D$ +17.3° (*c* 1.24, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.90 (m, 2H), 6.91 (m, 2H), 5.52 (d, J = 11.9, 1H), 3.87 (m, 1H), 3.84 (s, 3H), 3.16 (m, 1H), 2.08 (m, 1H), 1.79 (m, 1H), 1.56 (m, 2H), 1.44 (br s, 11H); ^{13}C NMR ($CDCl_3$) δ 199.2, 163.3, 155.8, 130.5, 128.6, 113.7, 79.90, 56.67, 55.45, 42.61, 28.35, 26.52, 25.03, 19.90. Anal. ($C_{18}H_{25}NO_4$) C, H, N.

(2*S*)-*N*-(*tert*-Butyloxycarbonyl)piperidin-2-yl 4-methoxyphenyl ketone (13): 56% yield as a white solid; mp 97−99 °C; $[\alpha]^{20}_D$ −17.9° (*c* 1.33, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.90 (m, 2H), 6.90 (m, 2H), 5.52 (d, J = 12.0, 1H), 3.87 (m, 1H), 3.84 (s, 3H), 3.16 (m, 1H), 2.08 (m, 1H), 1.79 (m, 1H), 1.56 (m,

2H), 1.44 (br s, 11H); ^{13}C NMR ($CDCl_3$) δ 199.2, 163.3, 155.8, 130.6, 128.5, 113.7, 79.91, 56.67, 55.45, 42.58, 28.36, 26.50, 25.11, 19.96. Anal. ($C_{18}H_{25}NO_4$) H, N; C: calcd, 67.69; found, 67.10.

1-[(2*R*)-*N*-(*tert*-Butyloxycarbonyl)piperidin-2-yl]-1-phenylethene (8). To a suspension of methyltriphenylphosphonium bromide (230 mg, 0.644 mmol) in THF (1.0 mL) was added solid potassium *tert*-butoxide (72.2 mg, 0.644 mmol), and the resulting yellow suspension was allowed to stir for 10 min. A solution of (*R*)-**7** (124 mg, 0.429 mmol) in THF (2.0 mL) was then added dropwise via syringe and the reaction allowed to proceed for 5 min. The reaction was quenched with H_2O (1.0 mL) and suspended between EtOAc (15 mL) and H_2O (15 mL). The aqueous layer was extracted with EtOAc (2 × 15 mL). The combined EtOAc layers were dried, filtered, and evaporated to an oil which was then filtered though a plug of silica gel eluting with 9% EtOAc in hexanes to give 115 mg (93%) of (*R*)-**8** as a colorless oil: $[\alpha]^{20}_D$ −28.3° (*c* 1.16, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 3H), 7.27 (m, 2H), 5.26 (br s, 2H), 5.04 (s,-1H), 3.95 (m, 1H), 2.89 (t, *J* = 10, 1H), 1.78 (d, *J* = 2.9, 1H), 1.62 (m, 2H), 1.45 (s, 9H), 1.26 (br s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.4, 148.2, 141.4, 128.2, 127.3, 127.0, 124.4, 114.1, 79.42, 40.27, 28.44, 26.81, 25.46, 19.18. Anal. ($C_{18}H_{25}NO_2$) C, H, N.

1-(2*S*)-*N*-(*tert*-Butyloxycarbonyl)piperidin-2-yl]-1-phenylethene (8): 90% yield as a colorless oil; $[\alpha]^{20}_D$ +26.6° (*c* 1.59, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 3H), 7.27 (m, 2H), 5.26 (br s, 2H), 5.03 (s, 1H), 3.96 (m, 1H), 2.89 (t, *J* = 8.9, 1H), 1.78 (d, *J* = 3.2), 1H), 1.63 (m, 2H), 1.45 (s, 9H), 1.39 (br s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.3, 148.1, 141.3, 128.1, 127.2, 126.9, 124.2, 114.0, 79.32, 40.17, 28.33, 26.69, 25.33, 19.05. Anal. ($C_{18}H_{25}NO_2$) C, H, N.

1-[(2*R*)-*N*-(*tert*-Butyloxycarbonyl)piperidin-2-yl]-1-(4-bromophenyl)ethene (11): 95% yield as a colorless oil: $[\alpha]^{20}_D$ −9.21° (*c* 3.28, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.43 (m, 2H), 7.20 (m, 2H), 5.27 (br s, 2H), 5.07 (s, 1H), 3.86 (d, *J* = 3.0, 1H), 2.82 (m, 1H), 1.83 (m, 1H), 1.63 (m, 2H), 1.45 (s, 9H), 1.41 (br s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.3, 147.3, 140.2, 132.0, 131.3, 128.7, 121.3, 114.8, 79.61, 40.34, 28.46, 26.72, 25.40, 19.15. Anal. ($C_{18}H_{24}NO_2Br$) C, H, N.

1-[(2*S*)-*N*-(*tert*-Butyloxycarbonyl)piperidin-2-yl]-1-(4-bromophenyl)ethene (11): 93% yield as a colorless oil; $[\alpha]^{20}_D$ +7.55° (*c* 2.86, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.43 (m, 2H), 7.20 (m, 2H), 5.27 (br s, 2H), 5.07 (s, 1H), 3.86 (d, *J* = 3.0, 1H), 2.82 (m, 1H), 1.84 (m, 1H), 1.63 (m, 2H), 1.46 (s, 9H), 1.36 (br s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.3, 147.2, 140.2, 132.0, 131.3, 128.7, 121.3, 114.8, 79.61, 40.34, 28.47, 26.69, 25.43, 19.15. Anal. ($C_{18}H_{24}NO_2Br$) H, N; C: calcd, 59.02; found, 59.54.

1-[(2*R*)-*N*-(*tert*-Butyloxycarbonyl)piperidin-2-yl]-1-(4-methoxyphenyl)ethene (14): 98% yield as a colorless oil; $[\alpha]^{20}_D$ −22.7° (*c* 2.87, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 2H), 6.87 (m, 2H), 5.25 (br s, 2H), 5.01 (s, 1H), 3.94 (m, 1H), 3.82 (s, 3H), 2.90 (m, 1H), 1.83 (m, 1H), 1.63 (m, 2H), 1.49 (br s, 12H); ^{13}C NMR ($CDCl_3$) δ 158.9, 155.4, 147.5, 133.7, 128.0, 113.5, 113.1, 79.32, 55.19, 53.51, 40.24, 28.40, 26.75, 25.43, 19.12. Anal. ($C_{19}H_{27}NO_3$) C, H, N.

1-(2*S*)-*N*-(*tert*-Butyloxycarbonyl)piperidin-2-yl]-1-(4-methoxyphenyl)ethene (14): 96% yield as a colorless oil; $[\alpha]^{20}_D$ +25.6° (*c* 1.07, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.28 (m, 2H), 6.87 (m, 2H), 5.24 (br s, 2H), 5.05 (s, 1H), 3.95 (m, 1H), 3.81 (s, 3H), 2.92 (m, 1H), 1.83 (m, 1H), 1.60 (m, 2H), 1.48 (br s, 12H); ^{13}C NMR ($CDCl_3$) δ 158.9, 155.4, 147.5, 133.7, 128.0, 113.5, 113.0, 79.32, 55.19, 53.60, 40.27, 28.40, 26.75, 25.43, 19.12. Anal. ($C_{19}H_{27}NO_3$) C, H, N.

(1*R*)-1-[(2*R*)-*N*-(*tert*-Butyloxycarbonyl)piperidin-2-yl]-1-phenyl-2-hydroxyethane and (1*S*)-1-[(2*R*)-*N*-(*tert*-Butyloxycarbonyl)piperidin-2-yl]-1-phenyl-2-hydroxyethane (9). To a solution of (*R*)-**8** (115 mg, 0.401 mmol) in THF (2.0 mL) was added 1.0 M BH_3·THF (802 μL, 0.802 mmol) dropwise at room temperature via syringe over ∼5 min. The reaction mixture was then stirred for 4 h after which H_2O (1.0 mL), 3 N NaOH (1.0 mL), and 30% H_2O_2 (2.0 mL) were added consecutively. Stirring was continued overnight. The resulting mixture was suspended between EtOAc (20 mL) and H_2O (15 mL), and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined EtOAc layers were dried, filtered, and evaporated to an oil which was purified by silica gel chomatography eluting with 16−20% EtOAc in hexanes. The less polar (1*R*,2*R*)-**9** was obtained as a white solid (78 mg, 64% yield): mp 80−81 °C; $[\alpha]^{20}_D$ +12.4° (*c* 2.20, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.29 (m, 5H), 4.60 (d, *J* = 12, 1H), 4.00 (d, *J* = 13, 1H), 3.70 (m, 2H), 3.52 (m, 2H), 3.03 (d, *J* = 12, 2H), 2.81 (t, *J* = 11, 1H), 1.60 (m, 2H), 1.46 (s, 9H), 1.39 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 156.5, 141.3, 128.9, 128.6, 126.8, 80.39, 63.54, 50.33, 45.88, 39.92, 28.49, 26.09, 25.43, 18.88. The more polar (1*S*,2*R*)-**9** (30 mg, 25% yield) was obtained as a colorless oil: $[\alpha]^{20}_D$ +52.3° (*c* 1.06, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 5H), 4.57 (m, 1H), 3.87 (m, 3H), 3.27 (m, 1H), 2.61 (m, 1H), 1.83 (m, 1H), 1.70 (m, 3H), 1.36 (s, 9H), 1.34 (br s, 2H).

(1*S*)-1-[(2*S*)-*N*-(*tert*-Butyloxycarbonyl)piperidin-2-yl]-1-phenyl-2-hydroxyethane and (1*R*)-1-[(2*S*)-*N*-(*tert*-Butyloxycarbonyl)piperidin-2-yl]-1-phenyl-2-hydroxyethane (9): 61% yield of (1*S*,2*S*)-**9** as a white solid, mp 78−80 °C; $[\alpha]^{20}_D$ −11.1° (*c* 1.32, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 5H), 4.61 (d, *J* = 11, 1H), 4.01 (d, *J* = 12, 1H), 3.71 (m, 2H), 3.54 (m, 2H), 3.04 (d, *J* = 11, 2H), 2.82 (t, *J* = 12, 1H), 1.61 (m, 2H), 1.48 (s, 9H), 1.28 (br s, 2H); ^{13}C NMR ($CDCl_3$) δ 156.2, 141.2, 128.6, 128.3, 126.5, 80.10, 50.17, 45.67, 39.70, 28.28, 25.88, 25.23, 18.67. Anal. ($C_{18}H_{27}NO_3$) C, H, N.

(1*S*,2*R*)-**9** was obtained as an oil in 21% yield: $[\alpha]^{20}_D$ −52.7° (*c* 1.09, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.37 (m, 5H), 4.58 (m, 1H), 3.88 (m, 3H), 3.31 (m, 1H), 2.67 (m, 1H), 1.85 (m, 1H), 1.73 (m, 3H), 1.35 (s, 9H), 1.32 (br s, 2H). Anal. ($C_{18}H_{27}NO_3$) C, H, N.

(1*R*)-1-[(2*R*)-*N*-(*tert*-Butyloxycarbonyl)piperidin-2-yl]-1-(4-bromophenyl)-2-hydroxyethane (12): 58% yield as a white solid; mp 117−118 °C; $[\alpha]^{20}_D$ +7.28° (*c* 3.09, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.43 (m, 2H), 7.27 (m, 2H), 4.59 (d, *J* = 12, 1H), 4.04 (d, *J* = 13, 1H), 3.73 (m, 2H), 3.51 (t, *J* = 12, 1H), 3.09 (d, *J* = 12, 1H), 2.85 (t, *J* = 13, 1H), 1.64 (br s, 1H), 1.50 (s, 9H), 1.47 (br s, 2H), 1.28 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 156.6, 140.5, 131.6, 130.6, 120.6, 80.66, 63.18, 50.10, 45.25, 39.98, 28.51, 26.08, 25.38, 18.87. Anal. ($C_{18}H_{26}NO_3Br$) C, H, N.

(1*S*)-1-[(2*S*)-*N*-(*tert*-Butyloxycarbonyl)piperidin-2-yl]-1-(4-bromophenyl)-2-hydroxyethane (12): 56% yield as a white solid; mp 114−117 °C; $[\alpha]^{20}_D$ −7.18° (*c* 3.51, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.44 (m, 2H), 7.27 (m, 2H), 4.59 (d, *J* = 12, 1H), 4.04 (d, *J* = 13, 1H), 3.71 (m, 2H), 3.51 (t, *J* = 12, 1H), 3.02 (d, *J* = 12, 1H), 2.82 (t, *J* = 13, 1H), 1.59 (br s, 1H), 1.50 (s, 9H), 1.47 (br s, 2H), 1.26 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 156.6, 140.5, 131.6, 130.6, 120.6, 80.66, 63.17, 50.08, 45.23, 39.99, 28.50, 26.11, 25.40, 18.85. Anal. ($C_{18}H_{26}NO_3Br$) C, H, N.

(1*R*)-1-[(2*R*)-*N*-(*tert*-Butyloxycarbonyl)piperidin-2-yl]-1-(4-methoxyphenyl)-2-hydroxyethane (15): 62% yield as a white solid; mp 115−117 °C; $[\alpha]^{20}_D$ +4.12° (*c* 1.31, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.37 (m, 2H), 6.94 (m, 2H), 4.67 (d, *J* = 11, 1H), 4.12 (d, *J* = 13, 1H), 3.87 (s, 3H), 3.80 (m, 2H), 3.60 (br s, 2H), 3.12 (d, *J* = 10, 1H), 2.93 (t, *J* = 11, 1H), 1.71 (m, 1H), 1.58 (s, 9H), 1.49 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 158.3, 156.3, 133.3, 129.6, 113.9, 80.23, 63.57, 55.12, 50.41, 44.86, 39.82, 28.40, 25.95, 25.36, 18.79. Anal. ($C_{19}H_{29}NO_4$) C, H, N.

(1*S*)-1-[(2*S*)-*N*-(*tert*-Butyloxycarbonyl)piperidin-2-yl]-1-(4-methoxyphenyl)-2-hydroxyethane (15): 64% yield as a white solid; mp 116−117 °C: $[\alpha]^{20}_D$ −4.18° (c 1.22, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.37 (m, 2H), 6.94 (m, 2H), 4.66 (d, *J* = 10, 1H), 4.11 (d, *J* = 12, 1H), 3.86 (s, 3H), 3.80 (m, 2H), 3.60 (br s, 2H), 3.12 (d, *J* = 11, 1H), 2.92 (t, *J* = 11, 1H), 1.70 (m, 1H), 1.58 (s, 9H), 1.44 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 158.3, 156.3, 133.3, 129.6, 113.9, 80.23, 63.57, 55.13, 50.42, 44.86, 39.82, 28.41, 25.95, 25.37, 18.79. Anal. ($C_{19}H_{29}NO_4$) C, H, N.

(2*R*,2′*R*)-Methylphenidate Hydrochloride (1). (1*R*,2*R*)-Alcohol **9** (228 mg, 0.748 mmol) was dissolved in DMF (3.0 mL), and PDC (984 mg, 2.62) was added. After 17 h of stirring, the reaction was quenched with H_2O (40 mL) and the resulting mixture extracted with Et_2O (6 × 20 mL). Combined Et_2O layers were then extracted with 0.5 N NaOH (4 × 30 mL) and the alkaline solution brought to pH = 2.0 with 3 N HCl. A white precipitate formed and was extracted into EtOAc (4 ×

30 mL) which was dried, filtered, and evaporated under reduced pressure to give a crude colorless oil (194 mg).

A portion (180 mg) of the crude oil was treated with excess diazomethane in ether (10 mL). The solution was evaporated to a light yellow oil which was stirred in 3 N methanolic HCl (10 mL) at room temperature overnight. Evaporation under reduced pressure provided a crude off-white solid which was recrystallized from EtOH/Et_2O to give 124 mg of (2*R*,2′*R*)-**1** as a white solid (67% yield from (1*R*,2*R*)-**9**): mp 221−223 °C; $[\alpha]^{20}_D$ +82.6° (*c* 1.09, MeOH); ^{1}H NMR (CD_3OD) δ 7.38 (m, 2H), 7.30 (m, 3H), 3.89 (m, 2H), 3.73 (s, 3H), 3.47 (d, *J* = 12.6, 1H), 3.31 (s, 1H), 3.11 (t, *J* = 11.2, 1H), 1.78 (m, 3H), 1.48 (m, 3H); ^{13}C NMR (CD_3OD) δ 173.4, 135.4, 130.5, 129.8, 59.35, 55.39, 53.52, 46.79, 27.73, 23.43, 22.95; HRMS calcd for $C_{14}H_{19}NO_2$ (MH^+) 234.1495, found 234.1509.

(2*S*,2′*R*)-Methylphenidate Hydrochloride (1): 73% yield as a white solid from (1*S*,2*R*)-**9**; mp 218−219 °C; $[\alpha]^{20}_D$ −94.5° (*c* 1.59, MeOH); ^{1}H NMR (CD_3OD) δ 7.44 (m, 5H), 4.03 (d, *J* = 9.1, 1H), 3.78 (t, *J* = 8.2, 1H), 3.70 (s, 3H), 3.32 (m, 1H), 3.00 (t, *J* = 13, 1H), 2.10 (m, 1H), 1.91 (m, 2H), 1.71 (m, 3H); ^{13}C NMR (CD_3OD) δ 172.6, 134.0, 130.8, 130.3, 130.0, 59.52, 55.92, 53.14, 47.01, 28.78, 23.31, 23.01; HRMS calcd for $C_{14}H_{19}NO_2$ (MH^+) 234.1495, found 234.1495.

(2*S*,2′*S*)-Methylphenidate hydrochloride (1): 67% yield as a white solid from (1*S*,2*S*)-**9**; mp 219−221 °C; $[\alpha]^{20}_D$ −81.8° (*c* 1.38, MeOH); ^{1}H NMR (CD_3OD) δ 7.41 (m, 2H), 7.31 (m, 3H), 3.88 (m, 2H), 3.73 (s, 3H), 3.45 (d, *J* = 11, 1H), 3.11 (t, *J* = 13, 1H), 1.82 (m, 3H), 1.51 (m, 3H); ^{13}C NMR (CD_3OD) δ 173.2, 135.3, 130.4, 129.6, 59.20, 55.21, 53.40, 46.64, 27.55, 23.24, 22.80; HRMS calcd for $C_{14}H_{19}NO_2$ (MH^+) 234.1495, found 234.1496. Anal. ($C_{14}H_{19}NO_2$·HCl·0.14H_2O) C, H, N.

(2*R*,2′*S*)-Methylphenidate hydrochloride (1): 68% yield as a white solid from (1*R*,2*S*)-**9**; mp 216−219 °C:;$[\alpha]^{20}_D$ +92.3° (*c* 1.11, MeOH); ^{1}H NMR (CD_3OD) δ 7.45 (m, 5H), 3.97 (d, *J* = 9.3, 1H), 3.81 (t, *J* = 9.8, 1H), 3.73 (s, 3H), 3.35 (m, 1H), 3.01 (t, *J* = 13, 1H), 2.13 (m, 1H), 1.95 (m, 2H), 1.72 (m, 3H); ^{13}C NMR (CD_3OD) δ 172.5, 134.1, 130.7, 130.2, 130.0, 59.52, 55.86, 53.14, 46.99, 28.65, 23.22, 22.99; HRMS calcd for $C_{14}H_{19}NO_2$ (MH^+) 234.1495, found 234.1493. Anal. ($C_{14}H_{19}NO_2$·HCl·0.16H_2O) C, H, N.

(2*R*,2′*R*)-*p*-(Bromomethyl)phenidate hydrochloride (2): 62% yield as a white solid from (2*R*,2′*R*)-**12**; mp 222−223 °C; $[\alpha]^{20}_D$ +69.1° (*c* 3.09, CH_2Cl_2); ^{1}H NMR (CD_3OD) δ 7.56 (d, *J* = 8.4, 2H), 7.26 (d, *J* = 8.4, 2H), 3.99 (d, *J* = 9.8, 1H), 3.84 (t, *J* = 9.9, 1H), 3.73 (s, 3H), 3.46 (d, *J* = 13, 1H), 3.11 (t, *J* = 13, 1H), 1.79 (m, 3H), 1.49 (m, 3H); ^{13}C NMR (CD_3OD) δ 172.8, 134.4, 133.5, 131.6, 123.6, 58.93, 54.60, 53.56, 46.67, 27.59, 23.25, 22.76; HRMS calcd for $C_{14}H_{18}NO_2Br$ (MH^+) 312.0599, found 312.0614.

(2*S*,2′*S*)-*p*-(Bromomethyl)phenidate hydrochloride (2): 58% yield as a white solid from (2*S*,2′*S*)-**12**: mp 213−216 °C; $[\alpha]^{20}_D$ −64.6° (*c* 1.90, CH_2Cl_2); ^{1}H NMR (CD_3OD) δ 7.57 (d, *J* = 8.4, 2H), 7.25 (d, *J* = 8.4, 2H), 3.94 (d, *J* = 9.8, 1H), 3.83 (t, *J* = 11, 1H), 3.74 (s, 3H), 3.45 (d, *J* = 13, 1H), 3.10 (t, *J* = 13, 1H), 1.78 (m, 3H), 1.48 (m, 3H); ^{13}C NMR (CD_3OD) δ 172.8, 134.4, 133.5, 131.6, 123.7, 58.96, 54.63, 53.56, 46.70, 27.68, 23.29, 22.76; HRMS calcd for $C_{14}H_{18}NO_2Br$ (MH^+) 312.0599, found 312.0577.

(2*R*,2′*R*)-*p*-(Methoxymethyl)phenidate hydrochloride (3): 64% yield as a white solid from (2*R*,2′*R*)-**15**; mp 226−228 °C; $[\alpha]^{20}_D$ +86.6° (*c* 1.98, MeOH); ^{1}H NMR (CD_3OD) δ 7.22 (d, *J* = 8.6, 2H), 6.95 (d, *J* = 8.6, 2H), 3.86 (d, *J* = 10, 1H), 3.79 (s, 3H), 3.77 (m, 1H), 3.72 (s, 3H), 3.44 (d, *J* = 11, 1H), 3.10 (t, *J* = 13, 1H), 1.80 (m, 3H), 1.48 (m, 3H); ^{13}C NMR (CD_3OD) δ 173.5, 161.4, 130.7, 126.9, 115.7, 59.35, 55.83, 54.51, 53.34, 46.64, 27.65, 23.38, 22.83; HRMS calcd for $C_{15}H_{21}NO_3$ (MH^+) 264.1600, found 264.1625. Anal. ($C_{15}H_{21}NO_3$·HCl) H, N; C: calcd, 60.09; found, 59.52.

(2*S*,2′*S*)-*p*-(Methoxymethyl)phenidate hydrochloride (3): 60% yield as a white solid from (2*S*,2′*S*)-**15**; mp 226−228 °C; $[\alpha]^{20}_D$ −87.7° (*c* 1.38, MeOH); ^{1}H NMR (CD_3OD) δ 7.23 (d, *J* = 8.6, 2H), 6.93 (d, *J* = 8.6, 2H), 3.96 (d, *J* = 10, 1H), 3.77 (br s, 4H), 3.71 (s, 3H), 3.47 (d, *J* = 12, 1H), 3.11 (t, *J* = 12, 1H), 1.82 (m, 3H), 1.45 (m, 3H); ^{13}C NMR (CD_3OD) δ 173.5, 161.2, 130.7, 127.0, 115.7, 59.28, 55.86, 54.37, 53.36, 46.61, 27.46, 23.22, 22.83; HRMS calcd for $C_{15}H_{21}NO_3$ (MH^+) 264.1600, found 264.1621.

Assessment of Enantiomeric Purity of *N*-Boc-pipecolic Acid (5). Acid **5** (10 mg, 44 μmol) was dissolved in CH_2Cl_2 (200 μL) containing TEA (18.4 μL, 131 μmol). *l*-(−)-α-Phenylethylamine (6.8 mL, 53 μmol) of >98% optical purity and BOP (23.2 mg, 52 μmol) were added, and the reaction was stirred in a sealed vial for 60 min. The reaction mixture was washed sequentially with 1.0 M HCl (500 μL) and saturated $NaHCO_3$ (500 μL). The organic layer (10 μL) was diluted in amyl acetate (10 mL), and a 1.0 μL aliquot was analyzed by capillary GC−MS under the conditions described above which allowed baseline separation of the enantiomers of **5**. By this method, both enantiomers of **5** were found to be >98% enantiomerically pure.

Optical Purity of Chiral MPH and Its Para-Substituted Analogues. The enantiomeric dispositions of each of the threo enantiomers of **1**, **2**, and **3** prepared in our laboratory were assessed by gas chromatographic derivatization technique. Each hydrochloride salt of the *d*- and *l*-threo enantiomers (2 μg) was dissolved in 2.0 mL of 10% aqueous Na_2CO_3 and chilled on ice for 10 min. A 0.1 M solution of (*S*)-methoxy-(trifluoromethyl)phenylacetyl chloride[29] in CH_2Cl_2 (25 μL) was added and the solution vortexed for 1 min. The reaction was allowed to proceed at room temperature for 1 h. Cyclohexane (4.0 mL) was added, and the tubes were shaken for 10 min. After a brief centrifugation to separate the layers, the top cyclohexane layer was transferred into a clean tube, dried in a Savant speed vac concentrator, and reconstituted in amyl acetate (100 μL). The samples were transferred to crimp-top vials with 100 μL volume silanized inserts and injected into a gas chromatography−mass spectrometer (GC−MS). MSD was set for selective ion monitoring of peaks at *m*/*e* 84, 189, and 300. The enantiomers of each racemic pair were baseline resolved to give >99% optical purity for all *d*-threo enantiomers and 96% optical purity for all *l*-threo enantiomers. The retention times for the (S)-MTPA derivatives of these compounds were: *d*-threo **1**, 20.91 min; *l*-threo **1**, 20.79 min; *d*-threo **2**, 24.22 min; *l*-threo **2**, 24.03 min; *d*-threo **3**, 23.68 min; *l*-threo **3**, 23.51 min.

Pharmacology. Male Sprague−Dawley rats (200−270 g) were obtained from Hilltop Animal (Scottdale, PA) for synaptosomal assays or from Zivic-Miller Laboratories (Zelienople, PA) for locomotor studies. [^{3}H]Dihydroxyphenylethylamine (specific activity 37.5 Ci/mmol), [^{3}H]*l*-norepinephrine (specific activity 55.5 Ci/mmol), and [^{3}H]hydroxytryptamine binoxalate (specific activity 24.0 Ci/mmol) were purchased from New England Nuclear (Boston, MA). (*S*)-(+)-α-Methoxy(trifluoromethyl)phenylacetyl chloride (MTPC) of 98% ee was obtained from Aldrich Chemical Co. (Milwaukee, WI) and used as a 0.1 M solution in CH_2Cl_2.

Drug. Racemic **1** (Ritalin) was obtained from Ciba-Geigy. The enantiomers of **1** (MW = 269) and **2** (MW = 348) and **3** (MW = 301) substituted analogues were prepared by asymmetric synthesis and recrystallized as white hydrochloride salts.

Tissue Preparation. Male Sprague−Dawley rats (240−270 g) were killed by cervical dislocation. Their brains were rapidly removed and dissected on an ice-cold Petri dish into frontal cortical, temporal cortical, and striatal tissues. Frontal and temporal regions were suspended in a 25-volume dilution of Tris buffer (0.32 M sucrose, 1 mM Tris, and 10 mM glucose adjusted to pH 7.4 with HCl) while the striatal region was suspended in a 50-volume dilution of the same buffer. Homogenizations were performed with 10 up and down strokes in a Polytron homogenizer. Clearance between the Teflon pestle and the glass vessel was 0.025 cm. An S_1 fraction was obtained after centrifugation (1000*g* for 15 min at 4 °C) by carefully drawing off the supernatant from the pellet.

Neurotransmitter Uptake Studies. Uptake inhibition at various drug concentrations was assessed in triplicate with a final concentration of 25 nM, 50 nM, and 5 nM for [^{3}H]DA, [^{3}H]*l*-NE, and [^{3}H]5-HT, respectively. Nonspecific temperature

insensitive uptake was defined as the amount of radioactive uptake at 0 °C. Five different concentrations of drug were incubated along with tritiated amine, uptake buffer (145 mM NaCl, 3 mM KCl, 1.28 mM $CaCl_2$, 1.19 mM $MgCl_2$, 39 mM Trisma HCl, 11 nM glucose, and 50 nM pargyline), and 100 μL of crude synaptosomes in a final assay volume of 0.5 mL. Samples containing drug, radioactive neurotransmitter, and uptake buffer were preincubated with gentle agitation at 37 °C for 5 min at which point 100 μL of crude synaptosomal preparations were added, and the reaction was allowed to proceed at 37 °C for 5 min. Nonspecific transport was determined by carrying out the same procedures with tubes kept on ice. Uptake of radioactive amine was terminated by the addition of 5.0 mL of ice-cold 0.9% NaCl solution followed by rapid filtration with a Brandel Cell Harvester (Gaithersburg, MD) over glass-fiber filters (Whatman GF/B) presoaked with an aqueous solution of nonradioactive neurotransmitter. Samples and filter were washed twice with 5 mL of cold 0.9% NaCl solution. The filters were transferred to scintillation vials and heated with caps tightly sealed at 50 °C in 1.0 mL of Soluene-350 tissue solubilizer (Packard) for 60 min. After the samples were allowed to cool to room temperature, 15 mL of Opti-fluor scintillation fluid (Packard) was added, and the samples were kept in the dark for at least 4 h. The radioactivity was quantitated in a Beckman LS 5801 liquid scintillation counter with a counting efficiency of 45−50%. Temperature-sensitive uptake activity was obtained by subtracting radioactive counts for nonspecific transport at 0 °C from radioactive counts for samples at 37 °C.

Data Analysis. Data points from five different concentrations of drug were fit to a sigmoidal curve using the program TABLECURVE (Jandel Scientific). IC_{50} values were obtained by reading the values off the graph.

Locomotor Activity. Male Sprague−Dawley rats (200−250 g) were given food and water ad libitum. They were housed in pairs and maintained in a temperature-controlled colony room with a 12L:12D schedule. All testing was conducted one to 2 h after the beginning of a light cycle. Locomotor activity was measured in an open-field box with dimensions of 30.5 cm width × 43.5 cm length × 27.5 cm height fitted with four infrared sources and detectors. The sources were positioned on two of the four walls opposite their respective detectors which divided the field into nine rectangles roughly equal in area. Male Sprague−Dawley rats were allowed to adapt to the locomotor box prior to drug treatment. The animals were then injected ip with a 37 μmol/kg dose of drug as the hydrochloride salt dissolved in 1.0 mL/kg saline using a 26-gauge $^1/_2$-in. needle. For lower dose studies of **1** and **2**, doses of 1.0 and 2.5 mg/kg of the hydrochloride salts were administered in like manner. Each interruption of the infrared beams was registered as a single activity count, and the recording was conducted at 10-min intervals over a 180-min period. The tabulated counts from all four detectors were added to give total activity for each 10-min interval.

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Supporting Information Available: Elemental analyses data for all compounds and experimental procedures for studies reported in Tables 1 and 2 (5 pages). Ordering information is given on any current masthead page.

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